Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

Mycobacterium avium Complex Disease (Last updated November 6, 2013; last reviewed November 6, 2013)

Panel's Recommendations
- Routine screening of respiratory or gastrointestinal specimens for *Mycobacterium avium* complex (MAC) microorganisms is not recommended **(BIII)**, but a blood culture for MAC should be obtained to rule out disseminated disease before initiating prophylaxis **(AIII)**.   - Prophylaxis with either clarithromycin or azithromycin should be offered to HIV-infected children who have advanced immunosuppression **(AII)**.   - Children aged <1 year: <750 cells/mm^3 - Children aged 1 to <2 years: <500 cells/mm^3 - Children aged 2 to <6 years: <75 cells/mm^3 - Children aged ≥6 years: <50 cells/mm^3 Discontinuing Primary Prophylaxis: - Primary prophylaxis can be discontinued in HIV-infected children aged ≥2 years receiving stable combination antiretroviral therapy (cART) for ≥6 months and experiencing sustained (>3 months) CD4 T lymphocyte (CD4) cell count recovery well above the age-specific target for initiation of prophylaxis (i.e., as in adults, >100 cells/mm^3 for children aged ≥6 years **(AI)**; and >200 cells/mm^3 for children aged 2 to <6 years) **(BII*)**.   Treating Disease: - Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended **(BIII)**. Combination therapy with a minimum of two drugs (e.g., clarithromycin or azithromycin plus ethambutol) is recommended to prevent or delay the emergence of resistance **(AI*)**. Some experts use clarithromycin as the preferred first agent **(AI*)**, reserving azithromycin for patients with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern **(AII*)**.   - Use of rifabutin as a third drug added to the macrolide/ethambutol regimen is controversial. Some experts would add rifabutin as a third drug to the clarithromycin/ethambutol regimen, particularly in the absence of cART and in the presence of high mycobacterial counts **(CIII)**; however, drug interactions should be checked carefully, and more intensive toxicity monitoring may be warranted with such combination therapy **(AIII)**. Other experts recommend against using this third agent in children because of rifabutin's increased cytochrome P450 activity, which leads to increased clearance of other drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, and the potential for increased toxicity associated with concomitant administration of drugs **(CIII)**.   - Treatment failure is defined as the absence of clinical response and the persistence of mycobacteremia after 8 to 12 weeks of treatment. Repeat susceptibility testing of MAC isolates is recommended in this situation, and a new multidrug regimen of two or more drugs not previously used and to which the isolate is susceptible should be administered **(AIII)**. Drugs that should be considered for this scenario include rifabutin, amikacin, and a quinolone.   Secondary Prophylaxis: - Children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence **(AII*)**. Secondary prophylaxis typically consists of continued multidrug therapy used in treatment of disease.   - Some experts recommend discontinuation of therapy in HIV-infected children who meet **all** of the following criteria: - Aged ≥2 years and have completed ≥12 months of treatment for MAC;   - Remain asymptomatic for MAC;   - Receiving stable cART (i.e., cART not requiring change for virologic or immunologic failure);   - Have sustained (≥6 months) CD4 count recovery well above the age-specific target for initiation of primary prophylaxis (i.e., as in adults, >100 cells/mm^3 for children aged ≥ 6 years **(AII*)** and >200 cells/mm^3 for children aged 2 to <6 years) **(CIII)**.   *Rating of Recommendations:* A = Strong; B = Moderate; C = Optional *Rating of Evidence:* I = One or more randomized trials <u>in children</u>† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials <u>in adults</u> with clinical outcomes and/or validated laboratory endpoints with accompanying data <u>in children</u>† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies <u>in children</u>† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies <u>in adults</u> with long-term clinical outcomes with accompanying data <u>in children</u>† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion † Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

Mycobacterium avium complex (MAC) refers to multiple related species of nontuberculous mycobacteria (NTM) (e.g., *Mycobacterium avium*, *Mycobacterium intracellulare*, and *Mycobacterium paratuberculosis*) that are widely distributed in the environment. Recent surveillance data have shown an increasing rate of MAC infection in some regions within the United States.[1] Comprehensive guidelines on the diagnosis, prevention, and treatment of nontuberculous mycobacterial diseases were published in 2007.[2] These guidelines highlight the tremendous advances in laboratory methods in mycobacteriology that have expanded the number of known NTM species from 50 in 1997 to 125 in 2006. In the United States, NTM infections outnumber *Mycobacterium tuberculosis* infections and have become an important cause of pulmonary morbidity in adults.[3]

MAC was the second most common opportunistic infection (OI) in HIV-infected children in the United States after *Pneumocystis jirovecii* pneumonia during the era before combination antiretroviral therapy (cART), but its incidence has greatly decreased from 1.3 to 1.8 episodes per 100 person-years during that time to 0.14 to 0.2 episodes per 100 person-years during the cART era.[4,5] MAC is ubiquitous in the environment and presumably is acquired by routine exposures through inhalation, ingestion, or inoculation.[6] A recent population-based study in Florida of adults and children associated soil exposure, along with black race and birth outside the United States, with MAC infection.[7] Respiratory and gastrointestinal (GI) colonization can act as portals from which infection can disseminate.[8]

MAC can appear as isolated lymphadenitis in both HIV-infected and HIV-uninfected children. Disseminated infection with MAC in pediatric HIV infection rarely occurs during the first year of life; its frequency increases with age and declining CD4 T lymphocyte (CD4) cell count, but can occur at higher CD4 counts in younger HIV-infected children than in older children or adults. It is a recognized complication of advanced immunologic deterioration among HIV-infected children.[6,9,10]

Clinical Manifestations

Respiratory symptoms are uncommon in HIV-infected children who have disseminated MAC, and isolated pulmonary disease is rare. Early symptoms can be minimal and may precede mycobacteremia by several weeks. Symptoms commonly associated with disseminated MAC infection in children include persistent or recurrent fever, weight loss or failure to gain weight, sweats, fatigue, persistent diarrhea, and persistent or recurrent abdominal pain. Mesenteric adenitis may mimic acute appendicitis. GI symptoms can occur alone or in combination with systemic findings. Lymphadenopathy, hepatomegaly, and splenomegaly may occur. Laboratory abnormalities include anemia, leukopenia, and thrombocytopenia. Although serum chemistries are usually normal, some children may have elevated alkaline phosphatase or lactate dehydrogenase levels. These signs and symptoms also are relatively common in the absence of disseminated MAC in HIV-infected children with advanced immunosuppression.

Diagnosis

Procedures used to diagnose MAC in children are the same as those used for HIV-infected adults.[11] MAC is definitively diagnosed by isolation of the organism from blood or from biopsy specimens from normally sterile sites (e.g., bone marrow, lymph node). Multiple mycobacterial blood cultures over time may be required to yield a positive result. The volume of blood sent for culture also influences yield, with increased volume leading to increased yield. Use of a radiometric broth medium or lysis-centrifugation culture technique can enhance recovery of organisms from blood.

Histology demonstrating macrophage-containing acid-fast bacilli is strongly indicative of MAC infection in a patient with typical signs and symptoms, but culture is essential to differentiate nontuberculous mycobacteria from *M. tuberculosis*, to determine which nontuberculous mycobacterium is causing infection, and to perform drug-susceptibility testing. Testing of MAC isolates for susceptibility to clarithromycin or

azithromycin is recommended **(BIII)**. The BACTEC™ method for radiometric susceptibility testing can be used. Resistance for clarithromycin is defined as a minimal inhibitory concentration ≥32 µg/mL and a minimal inhibitory concentration of ≥256 µg/mL for azithromycin.[12] As with tuberculosis testing, multiplex polymerase chain reaction systems have been developed for rapid identification and drug susceptibility testing, but these are currently only available in research laboratories.[13,14]

Prevention Recommendations

Preventing Exposure

MAC is ubiquitous in the environment. Available information does not support specific recommendations regarding exposure avoidance.[1] Person-to-person transmission is not believed to be common.

Preventing First Episode of Disease

The most effective way to prevent disseminated MAC among HIV-infected children is to preserve immune function through use of effective cART. HIV-infected children who have advanced immunosuppression should be offered prophylaxis against disseminated MAC disease according to the following CD4 count thresholds **(AII)**:[15,16]

- Children aged <1 year: <750 cells/mm^3
- Children aged 1 to <2 years: <500 cells/mm^3
- Children aged 2 to <6 years: <75 cells/mm^3
- Children aged ≥6 years: <50 cells/mm^3

For the same reasons that clarithromycin and azithromycin are the preferred prophylactic agents for adults, either one is recommended for prophylaxis in children **(AI*)**; oral suspensions of both agents are commercially available in the United States. Before prophylaxis is initiated, at-risk children should be evaluated for disseminated MAC disease, including obtaining a blood culture for MAC **(AIII)**. For children who cannot tolerate azithromycin or clarithromycin, rifabutin is an alternative prophylactic agent for MAC, although drug interactions and a lack of efficacy data in children limit its use **(CIII)**. Combination therapy for prophylaxis has not been shown to be cost effective and increases rates of adverse events, and therefore, generally should be avoided in children **(AIII)**.

Although detection of MAC in stool or the respiratory tract may precede disseminated disease, no data demonstrate a correlation between initiation of prophylaxis in patients with detectable organisms at these sites and reduced risk of developing disseminated MAC. Therefore, routine screening of respiratory or GI specimens for MAC is not recommended **(BIII)**.

Discontinuing Primary Prophylaxis

On the basis of both randomized controlled trials and observational data, primary prophylaxis for MAC can be safely discontinued in HIV-infected adults who respond to cART with an increase in CD4 count.[17,18] In a study of discontinuing OI prophylaxis among HIV-infected children whose CD4 percentages were ≥20% for those aged >6 years and ≥25% for those aged 2 to 6 years, 63 HIV-infected children discontinued MAC prophylaxis, and no MAC events were observed during ≥2 years of follow up.[19] On the basis of both these findings and data from studies in adults, primary prophylaxis can be discontinued in HIV-infected children aged ≥2 years receiving stable cART for ≥6 months who experience sustained (>3 months) CD4 cell recovery well above the age-specific target for initiation of prophylaxis (i.e., as in adults, >100 cells/mm^3 for children aged ≥6 years and >200 cells/mm^3 for children aged 2 to <6 years) **(BII*)**. No specific recommendations exist for discontinuing MAC prophylaxis in HIV-infected children aged <2 years.

Treatment Recommendations

Treating Disease

Disseminated MAC infection should be treated in consultation with a pediatric infectious disease specialist who has expertise in pediatric HIV infection **(AIII)**. Combination therapy of MAC with a minimum of 2 drugs is recommended to prevent or delay the emergence of resistance **(AI*)**.[20-23] Monotherapy with a macrolide results in emergence of high-level drug resistance within weeks.[24]

Improved immunologic status is important for controlling disseminated MAC disease; cART should be initiated in children with MAC disease who are antiretroviral (ARV) naive. However, the optimal time to start cART in this situation is unknown; many experts treat MAC with antimycobacterial therapy for 2 weeks before starting cART to try to minimize immune reconstitution inflammatory syndrome (IRIS), although whether this makes a difference is unknown **(CIII)**. For children already receiving cART, it should be continued and optimized with careful attention to potential drug interactions between the ARV and antimycobacterial drugs.

Initial MAC empiric therapy should include 2 or more drugs **(AI*)**: clarithromycin or azithromycin plus ethambutol.[25] Some experts use clarithromycin as the preferred first agent **(AI*)**, reserving azithromycin for patients with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern **(AII*)**.[26] Clarithromycin levels can be increased by protease inhibitors (PI) and decreased by efavirenz, but no data are available to recommend dose adjustments for children. Azithromycin is not metabolized by the cytochrome P450 (CYP450) system; therefore, it can be used without concern for significant drug interactions with PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Because a study in adults demonstrated a survival benefit with the addition of rifabutin to clarithromycin plus ethambutol, some experts would add rifabutin as a third drug to the clarithromycin/ethambutol regimen **(CIII)**;[23] however, drug interactions should be checked carefully, and more intensive toxicity monitoring may be warranted if such drugs are administered concomitantly **(AIII)**.[27] Because rifabutin increases CYP450 activity that leads to increased clearance of other drugs (e.g., PIs, NNRTIs), and toxicity might increase with concomitant administration of drugs, other experts recommend against using this third agent in children **(CIII)**. Guidelines and recommendations exist for dose adjustments necessary in adults treated with rifabutin and PIs, but the absence of data in children precludes extrapolating these to HIV-infected children undergoing treatment for disseminated MAC. No pediatric formulation of rifabutin exists, but the drug can be administered mixed with foods such as applesauce. It can also be compounded in a liquid formulation by a pharmacist. Limited safety data are available from 22 HIV-infected children (median age: 9 years) who received rifabutin in combination with 2 or more other antimycobacterial drugs for treatment of MAC for 1 to 183 weeks; doses ranged from 4 mg/kg to 18.5 mg/kg, and reported adverse effects were similar to those reported in adults.[28] The most commonly reported dose in children has been 5 mg/kg.

Therapy is typically prolonged and depends upon response and immune reconstitution as discussed under cessation of secondary prophylaxis.

Monitoring and Adverse Events, Including IRIS

Clinically, most patients improve substantially during the first 4 to 6 weeks of therapy. A repeat blood culture for MAC should be obtained 4 to 8 weeks after initiation of antimycobacterial therapy in patients who fail to respond clinically to their initial treatment regimen. Some experts would consider a repeat blood culture for all patients with an initial positive culture, regardless of clinical response to therapy. Improvement in fever can be expected within 2 to 4 weeks after initiation of appropriate therapy. However, for those with more extensive disease or advanced immunosuppression, clinical response may be delayed, and elimination of the organism from the blood may require up to 12 weeks of effective therapy.

IRIS in patients receiving MAC therapy during cART has been reported in HIV-infected adults and children.[29-32] New onset of systemic symptoms, especially fever or abdominal pain, leukocytosis, and focal

lymphadenitis (cervical, thoracic, or abdominal) associated with preexisting but relatively asymptomatic MAC infection has occurred after the start of cART. In addition, paradoxical worsening of systemic or local symptoms of MAC may occur as the immune system is reconstituted.

In children with very low CD4 counts, the decision to begin immediate cART must take into consideration not only the urgent need for rapid immunologic improvement, but also the possibility of IRIS due to MAC. If symptoms suggestive of MAC infection are present at the time of cART initiation, the clinician should evaluate for MAC and can consider treating for MAC presumptively. cART generally should be withheld until after the first 2 weeks of antimycobacterial therapy have been completed in patients with disseminated MAC disease who have not been treated previously with or are not receiving effective cART to reduce the risk of drug interactions and complications associated with IRIS and to lower the pill burden **(CIII)**. However, ART should be started as soon as possible after the first 2 weeks of antimycobacterial therapy in order to reduce the risk of developing additional AIDS-defining OIs, and to facilitate immune reconstitution and further improve the response to antimycobacterial therapy **(CIII)**. Children with moderate symptoms of IRIS can be treated symptomatically with nonsteroidal anti-inflammatory drugs (NSAIDs) or, if unresponsive to NSAIDS, a short course (such as 4 weeks) of systemic corticosteroid therapy while continuing to receive cART **(CIII)**.

Adverse effects from clarithromycin and azithromycin include nausea, vomiting, abdominal pain, abnormal taste, and elevations in liver transaminase levels or hypersensitivity reactions. The major toxicity associated with ethambutol is optic neuritis, with symptoms of blurry vision, central scotomata, and red-green color blindness, which usually is reversible and rare at doses of 15–25 mg/kg in children with normal renal function. Assessments of renal function, ophthalmoscopy, and (if possible) visual acuity and color vision should be performed before starting ethambutol and monitored regularly during treatment with the agent **(AIII)**. Use of ethambutol in very young children whose visual acuity cannot be monitored requires careful consideration of risks and benefits.[33,34]

Patients receiving clarithromycin plus rifabutin should be observed for the rifabutin-related development of leukopenia, uveitis, polyarthralgias, and pseudojaundice. Tiny, almost transparent, asymptomatic peripheral and central corneal deposits that do not impair vision have been observed in some HIV-infected children receiving rifabutin as part of a multidrug regimen for MAC.[28]

Managing Treatment Failure

Treatment failure is defined as the absence of clinical response and the persistence of mycobacteremia after 8 to 12 weeks of treatment. Repeat susceptibility testing of MAC isolates is recommended in this situation, and a new multidrug regimen of 2 or more drugs not previously used and to which the isolate is susceptible should be administered **(AIII)**. Drugs that should be considered for this scenario include rifabutin, amikacin, and a quinolone. Data from treating MAC in HIV-uninfected patients indicate that an injectable agent such as amikacin or streptomycin should be considered **(CIII)**.[2,3] Because dosing of these agents in children can be problematic, drug-resistant disseminated MAC should be treated with input from an expert in this disease **(AIII)**. Optimization of cART is an especially important adjunct to treatment of patients in whom initial MAC therapy has failed.

Preventing Recurrence

Children with a history of disseminated MAC should be given prophylaxis to prevent recurrence **(AII*)** until their immune systems are reconstituted.[35] Prophylaxis in this setting means continuation of multidrug therapy, because use of a single agent (clarithromycin or azithromycin) for secondary prophylaxis carries a high risk of inducing drug-resistant MAC infection.

Discontinuing Secondary Prophylaxis

On the basis of immune reconstitution data in adults[34,36] and data in children discontinuing primary prophylaxis, some experts recommend discontinuation of secondary prophylaxis in HIV-infected children aged ≥2 years who have completed ≥12 months of treatment for MAC, remain asymptomatic for MAC, and are receiving stable cART (i.e., cART not requiring change for viral or immune failure) and who have

sustained (≥6 months) CD4 count recovery well above the age-specific target for initiation of primary prophylaxis (as in adults, >100 cells/mm³ for children aged ≥6 years **(AII*)** and >200 cells/mm³ for children aged 2 to <6 years) **(CIII)**. Multidrug secondary prophylaxis should be reintroduced if the CD4 count falls below the age-related threshold.

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Dosing Recommendations for Prevention and Treatment of Mycobacterium avium Complex (MAC)
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Preventive Regimen			
Indication	**First Choice**	**Alternative**	**Comments/Special Issues**

Primary Prophylaxis	• Clarithromycin 7.5 mg/kg body weight (maximum 500 mg) by mouth orally twice daily, **or**
	• Azithromycin 20 mg/kg body weight (maximum 1200 mg) orally once weekly
		• Azithromycin 5 mg/kg body weight (maximum 250 mg) orally once daily
		• Children aged >5 years: rifabutin 300 mg orally once daily with food
			Primary Prophylaxis Indicated for Children:
			• Aged <1 year with CD4 count <750 cells/mm^3;
			• Aged 1 to <2 years with CD4 count <500 cells/mm^3;
			• Aged 2 to <6 years with CD4 count <75 cells/mm^3;
			• Aged ≥6 years with CD4 count <50 cells/mm^3
			
			Criteria for Discontinuing Primary Prophylaxis:
			• Do not discontinue in children age <2 years.
			• After ≥6 months of cART and:
			  • Aged 2 to <6 years with CD4 count >200 cells/mm^3 for >3 consecutive months
			  • Aged ≥6 years with CD4 count >100 cells/mm^3 for >3 consecutive months
			
			Criteria for Restarting Primary Prophylaxis:
			• Aged 2 to <6 years with CD4 count <200 cells/mm^3
			• Aged ≥6 years with CD4 count <100 cells/mm^3

Secondary Prophylaxis (Chronic Suppressive Therapy)	• Clarithromycin 7.5 mg/kg body weight (maximum 500 mg) orally twice daily, **plus** • Ethambutol 15–25 mg/kg body weight (maximum 2.5 g) orally once daily, **with or without** food • Children aged >5 years who received rifabutin as part of initial treatment: Rifabutin 5 mg/kg body weight (maximum 300 mg) orally once daily with food	• Azithromycin 5 mg/kg body weight (maximum 250 mg) orally once daily, **plus** • Ethambutol 15–25 mg/kg body weight (max 2.5 g) orally once daily, **with or without** food • Children aged >5 years who received rifabutin as part of initial treatment: Rifabutin 5 mg/kg body weight (maximum 300 mg) orally once daily with food.	Secondary Prophylaxis Indicated: • Prior disease Criteria for Discontinuing Secondary Prophylaxis *Fulfillment of All of the Following Criteria:* • Completed ≥6 months of cART • Completed ≥12 months MAC therapy • Asymptomatic for signs and symptoms of MAC • Aged 2 to <6 years with CD4 count >200 cells/mm^3 for ≥6 consecutive months • Aged ≥6 years with CD4 count >100 cells/mm^3 for ≥6 consecutive months Criteria for Restarting Secondary Prophylaxis: • Aged 2 to <6 years with CD4 count <200 cells/mm^3 • Aged ≥6 years with CD4 count <100 cells/mm^3

Preventive Regimen			
Indication	**First Choice**	**Alternative**	**Comments/Special Issues**
Treatment	<u>Initial Treatment (≥2 Drugs)</u>: • Clarithromycin 7.5–15 mg/kg body weight (maximum 500 mg/dose) orally twice daily **plus** ethambutol 15–25 mg/kg body weight (maximum 2.5 g/day) orally once daily followed by chronic suppressive therapy <u>For Severe Disease, Add</u>: • Rifabutin 10–20 mg/kg body weight (maximum 300 mg/day) orally once daily	<u>If Intolerant to Clarithromycin</u>: • Azithromycin 10–12 mg/kg body weight (maximum 500 mg/day) orally once daily <u>If Rifabutin Cannot Be Administered and a Third Drug is Needed in Addition to a Macrolide and Ethambutol, or if a Fourth Drug is Needed in Addition to Rifabutin for Patients with More Severe Symptoms or Disseminated Disease</u>: • Ciprofloxacin 10–15 mg/kg orally twice daily (maximum 1.5 g/day), or • Levofloxacin 500 mg daily once daily, or • Amikacin 15–30 mg/kg body weight IV in 1 or 2 divided doses (maximum 1.5 g/day)	Combination therapy with a minimum of 2 drugs is recommended for at least 12 months. Clofazimine is associated with increased mortality in HIV-infected adults and should not be used. Children receiving ethambutol who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and color discrimination. Fluoroquinolones (e.g., ciprofloxacin and levofloxacin) are not labeled for use in children aged <18 years because of concerns regarding potential effects on cartilage; use in younger individuals requires an assessment of potential risks and benefits Chronic suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial therapy.

Key to Acronyms: cART = combination antiretroviral therapy; CD4 = CD4 T lymphocyte; MAC = *Mycobacterium avium* Complex; IV = intravenous